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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,224	05/17/2005	Mahendra S. Rao	UT-0048	1620

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/502,224	RAO ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *5-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/22/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to papers filed January 26, 2007. Applicant's response to restriction requirement of January 10, 2007 has been entered. Claims 1, 2 and 6 have been amended. No claims were canceled, or newly added. Claims 1-10 are pending in the application.

Election/Restrictions

Applicants' election of Group I (claims 1-4), directed to a population of mammalian CD44 immunoreactive precursor cells that can generate astrocytes, a pharmaceutical composition comprising said cells ; and a method for isolating the same, with traverse, is acknowledged. Applicants' elections for the species of "laminin as the differentiation protein and fibronectin as a second differentiation protein, also with traverse, is further acknowledged. Claims 5-10 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicants have traversed the requirement for restriction, arguing that the unity of invention that was broken by citation of prior art teaching the special technical feature shared among inventions of Groups I and II, is directly contradicted by the International Search Report issued in the PCT application wherein all claims were searched and examined for patentability. Applicants' arguments have been fully considered, but are not found to be persuasive, because the fact that restriction was not required in the PCT application by a different examiner, does not preclude or negate the requirement in the U.S. National Stage. As stated in MPEP 1502.01, restriction between plural, distinct inventions is discretionary on the part of the examiner in utility patent applications. The restriction under PCT rules13.1 and 13.2 was proper, and Applicants have attempted to overcome the applied prior art of Woodbury by amending the base claim to state the claimed mammalian astrocyte restricted precursor cells were isolated from embryonic fetal tissue, or ES cell cultures. However, such language fails to overcome the art of Woodbury et al., because the claimed product is "a product by process", thus the claim is directed to the product and not the process of making the product. As such the technical feature of "CD44 immunoreactive mammalian precursor cells that generate astrocytes" remains unchanged, and is further taught by Woodbury.

Applicants then argue that as a search of prior art relating to all claims has already been performed in the corresponding PCT application, there is no burden on the Examiner by including all claims. Such is not found persuasive, because aside from the fact that Applicants have applied U.S. restriction practice in a case where restriction was properly applied under rules for Unity of Invention, U.S. restriction requirements are set forth for reasons of patentability distinction between each independent or distinct invention so as to warrant separate search and search burden as well as examination. In the instant case, the searches would not be co-extensive as evidenced by the different subject matter encompassed, such as treating damaged neural cells, and because simply providing a product fails to provide all the relevant art for any method of use as at best the claims are related here. Even though they are related in some way by subject matter, they are patentably distinct, as Groups II claims are directed to a treatment method, not required by claims of Group I.

Applicants should further note that as stated in MPEP 1893.03(d), any nonelected processes of making and/or using an allowable product should be considered for rejoinder following the practice set forth in MPEP § 821.04(b). Accordingly, should the instant claimed precursor cells be found allowable, they will be subject to rejoinder to claims 5-10.

As the requirement for restriction is still deemed proper, the election requirement is maintained and hereby made Final. Claims 5-10 are withdrawn from further consideration, as being drawn to a nonelected invention, Applicant timely traversed the restriction (election) requirement in the reply filed on January 26, 2007. Claims 1-4 are currently under examination.

Claim Rejections - 35 USC § 112 - Lack of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification is not enabling for a pure homogenous population of mammalian astrocyte restricted precursor cells, being CD44 immunoreactive and generating astrocytes but not oligodendrocytes, or a method of isolating the same from embryonic or fetal tissue, ES cell cultures, or glial restricted precursor cells, as claimed.

This rejection is based on issues, indicating an absence of an enabling disclosure for a precursor cell that is CD44 positive and can differentiated into astrocytes, but not oligodendrocytes, as claimed. The deficiency was identified by the Office after analysis of the disclosure provided in the instant application. In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404:

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The Office has analyzed the specification in direct accordance to the factors outlined in *In re Wands*. MPEP § 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection."

The instant specification does not provide an enabling disclosure for a pure homogenous population of mammalian astrocyte restricted precursor cells, being CD44 immunoreactive and generating astrocytes but not oligodendrocytes, or a method of isolating the same from embryonic or fetal tissue, ES cell cultures, or glial restricted precursor cells. When given their broadest reasonable interpretation in view of the as filed specification, the claims encompass a

composition of pure homogenous precursor cells that have the capacity to differentiate into and generate astrocytes but would not be able to differentiate and generate oligodendrocytes.

The specification states: "The astrocyte restricted precursor cells of the present invention do not express A2B5. Further these cells differ from stem and progenitor cell populations in their expression of CD44 and their ability to differentiate into astrocytes...but not oligodendrocytes" (lines 14-25, p. 4). The preceding is not accord with the observations in the working examples.

Examples 1-5 of the instant specification describe the culture of human neural progenitor cells from fetal tissue, obtained from a commercial source. To isolated human neuroepithelial precursor cells (hNEPs), the cells were cultured for 5 days and subjected to immunopanning and FACS sorting to remover NCAM+, NG2+ and A2B5+ cells (Example 2). The cells negative for said markers were then propagated and plated on fibronectin/laminin coated coverslips in various conditions to promote differentiation. For astrocytic differentiation, cells were cultured for 5 days in the presence of 10%FCS, and astrocytes were identified using antibodies to CD44, GFAP and S-100. For oligodendrocyte differentiation, cells were plated in a bFGF containing medium for two days and then switched to a medium containing PDGF and T3 for 7 days. To induce neuronal differentiation, cells were exposed to bFGF and NT3. After 5 days in culture, fixed cultures were stained using antibodies to beta-III tubulin to assess differentiation into neurons (Example 3, p. 17). Examples 6 and 7 describe the culture of human ES cell lines to form embryoid bodies that were subsequently plated on polylysine/fibronectin coated plates and treated with retinoic acid, hbFGF, hPDGF, hIGF-1, hNT-3 and hBDNF for several days. However, no data regarding the subsequent differentiation of the cells into any particular cell type or lineage is provided.

Therefore, at least for the human neuroepithelial progenitor cells, it is clear that following marker sorting, the same cell population may be differentiated to give rise to astrocytes, oligodendrocyte and neurons, depending on alterations in culture conditions. Hence, the human neuroepithelial progenitor cells are not astrocyte restricted, as they may differentiate into additional cells types. Moreover, the progenitor cells are capable of differentiation into oligodendrocytes, as taught by the specification, contrary to the language of the instant claims.

The prior art contains a number of examples wherein neuroprogenitor cells differentiate into astrocytes or other neural cells depending on culture conditions. For example, Raff et al. (Nature 303:390-396; 1983) describe a glial progenitor cell that develops into an astrocyte or an oligodendrocyte depending on culture medium (Abstract).

Carpenter (U.S. Patent No: 6,833,269; filed May 31, 2001), teaches methods for producing neural progenitor cells by culturing, expanding and differentiating embryonic stem cells into a variety of different neural phenotypes in a cocktail of growth conditions (Abstract). Specifically, human embryonic stem cells (hES) are maintained in a feeder-free system; the cells are expanded by serial passaging, removed and used formation of embryoid bodies (column 21). Carpenter states: "Typically, the differentiation takes place in a culture environment comprising a suitable substrate, and a nutrient medium to which the differentiation agents are added. Suitable substrates include solid surfaces coated with a positive charge, such as a basic amino acid, exemplified by poly-L-lysine and polyornithine. Substrates can be coated with extracellular matrix components, exemplified by fibronectin. Other permissive extracellular matrixes include Matrigel.RTM and laminin. Also suitable are combination substrates, such as poly-L-lysine combined with fibronectin, laminin, or both." (columns 11 and 12, bridging). Following immunosorting and magnetic separation, the "cells are maintained on plates coated with poly-lysine and laminin in DMEM/F12 (Biowhittaker) supplemented with N2 (Gibco 17502-014), B27 (Gibco 17504-010) and the factors indicated. Source of the factors is shown in Table 2." (column 22). Just before use, human bFGF is added to 4 ng/mL (WO 99/20741, Geron Corp.)" (columns 10-11, bridging). For differentiation, "Embryoid bodies made from human ES cells were maintained in 10 μM retinoic acid for 4 days, plated into a neural-supportive cocktail, and then passaged into medium containing 10 ng/mL NT-3 and 10 ng/mL BDNF." (column 5).

In Example 5, Carpenter et al. teach: "To generate terminally differentiated neurons, the first stage of differentiation was induced by forming embryoid bodies in FBS medium with or without 10 μM retinoic acid (RA). After 4 days in suspension, embryoid bodies were plated onto fibronectin-coated plates in defined medium supplemented with 10 ng/mL human EGF, 10 ng/mL human bFGF, 1 ng/mL human PDGF-AA, and 1 ng/mL human IGF-1. The embryoid bodies adhered to the plates, and cells began to migrate onto the plastic, forming a monolayer.

After 3 days, many cells with neuronal morphology were observed. The neural precursors were identified as cells positive for BrdU incorporation, nestin staining, and the absence of lineage specific differentiation markers. Putative neuronal and glial progenitor cells were identified as positive for polysialylated NCAM and A2B5...The cell populations were further differentiated by replating the cells in a medium containing none of the mitogens, but containing 10 ng/mL Neurotrophin-3 (NT-3) and 10 ng/mL brain-derived neurotrophic factor (BDNF). Neurons with extensive processes were seen after about 7 days." (column 28). Carpenter further teaches the differentiation of the cells in the absence of mitogens (claim 17). The method of Carpenter provides for the differentiation of pluripotent ES cells into cells of the neuronal or glial lineage. Precursor cells for either lineage, provide a source for generating additional precursor cells, neurons, astrocytes or oligodendrocytes (column 3; first paragraph), as well as neurons that include glial cells, astrocytes, dopaminergic cells and motor neurons (Abstract, column 19 and claim 18).

The prior art is however silent on mammalian neuroprogenitor cells that are astrocyte restricted and fail to generate oligodendrocytes. Regarding the limitation of CD44 marker present on the instantly claimed precursor cells Lodie et al. (Tissue Eng. 8:739-751; 2002) teach that in human bone marrow derived stem cells, CD44 expression is variable, and apparently dependent on serum concentration (Abstract). The authors further demonstrated that CD44 expression did not have an impact on the ability of the cells to ultimately differentiate toward the neural lineage and appeared to be dependent on serum concentration as demonstrated by other researchers (pp. 749-750, bridging).

As the teachings of the disclosure by Applicants fails to meet the limitations of the instant claims, and the prior art does not teach an astrocyte restricted precursor cell that does not generate oligodendrocytes, a person of skill in the art would need to engage in additional experimentation to develop the methodologies for discovering an astrocyte restricted precursor cell. Such further experimentation is regarded as undue and unpredictable, in view of the absence of sufficient guidance in either the instant specification or the prior art.

Therefore, in view of the lack of guidance provided by the specification for a precursor cell that is CD44 positive and can differentiate into astrocytes, but not oligodendrocytes, it would have required undue experimentation for one of skill in the art to practice applicant's invention as claimed. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4 are rejected under 35 U.S.C. 102(e) as being anticipated by Carpenter (U.S. Patent No.: 6,833,269; filed May 31, 2001).

The instant claims embrace a pure homogenous population of mammalian precursor cells isolated from mammalian embryonic or fetal tissue or mammalian embryonic stem (ES) cells cultures, being CD44 immunoreactive that may be differentiated to generate astrocytes. The claim language of "astrocyte restricted" is interpreted to be non-limiting because the ability of the cells to differentiate into astrocytes, but not oligodendrocytes is a consequence of culturing conditions, as taught by the instant specification (Example 3, p. 17).

Carpenter teaches methods for producing neural progenitor cells by culturing, expanding and differentiating embryonic stem cells into a variety of different neural phenotypes in a cocktail of growth conditions (Abstract).

Specifically, human embryonic stem cells (hES) are maintained in a feeder-free system on plates coated with Matrigel® in medium composed of 80% KO DMEM (knockout) and 20% serum replacement medium supplemented with 1% non-essential amino acids, 1mM glutamine, 0.1 mM β-mercaptoethanol and 4ng/ml bFGF, (the media conditioned by culturing embryonic fibroblasts) (column 21). The cells are expanded by serial passaging, removed and used formation of embryoid bodies (column 21).

Carpenter states: "Typically, the differentiation takes place in a culture environment comprising a suitable substrate, and a nutrient medium to which the differentiation agents are added." (columns 11 and 12, bridging). Following immunosorting and magnetic separation, the "cells are maintained on plates coated with poly-lysine and laminin in DMEM/F12 (Biowhittaker) supplemented with N2 (Gibco 17502-014), B27 (Gibco 17504-010) and the factors indicated. Source of the factors is shown in Table 2." (column 22).

In Example 5, Carpenter et al. teach: "To generate terminally differentiated neurons, the first stage of differentiation was induced by forming embryoid bodies in FBS medium with or without 10 μM retinoic acid (RA). After 4 days in suspension, embryoid bodies were plated onto fibronectin-coated plates in defined medium supplemented with 10 ng/mL human EGF, 10 ng/mL human bFGF, 1 ng/mL human PDGF-AA, and 1 ng/mL human IGF-1. After 3 days, many cells with neuronal morphology were observed. The neural precursors were identified as cells positive for BrdU incorporation, nestin staining, and the absence of lineage specific differentiation markers. Putative neuronal and glial progenitor cells were identified as positive for polysialylated NCAM and A2B5...The cell populations were further differentiated by replating the cells in a medium containing none of the mitogens, but containing 10 ng/mL Neurotrophin-3 (NT-3) and 10 ng/mL brain-derived neurotrophic factor (BDNF). Neurons with extensive processes were seen after about 7 days." (column 28). The method of Carpenter provides for the differentiation of pluripotent ES cells into cells of the neuronal or glial lineage. Precursor cells for either lineage, provide a source for generating additional precursor cells, neurons, astrocytes or oligodendrocytes (column 3; first paragraph), as well as neurons that include glial cells, astrocytes, dopaminergic cells and motor neurons (Abstract, column 19 and claim 18).

Carpenter additionally teach that the cells "described in this disclosure provides an unbounded supply of neuronal and glial cells for use in research, pharmaceutical development, and the therapeutic management of CNS abnormalities." (column 6), and that "the neural progenitor cells and terminally differentiated cells according to this invention can be supplied in the form of a pharmaceutical composition, comprising an isotonic excipient" (column 20). For general principles in medicinal formulations in stem cell transplantations, the reader is referred to publications incorporated by reference (column 20). The implantation of the cells into rat brains is described in Example 4.

While markers such as A2B5 are discussed by Capenter et al., CD44 immunoreactivity was not assessed by the authors. However, as stated above, CD44 expression is variable, and apparently dependent on serum concentration and culture conditions. Further the expression of CD44 is an inherent feature of the mammalian ES cell derived precursor cells of Carpenter et al. and must necessarily be present under the culture conditions of the instant invention. As stated in MPEP 2112: The express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. "The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." In re Napier, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir.1995) (affirmed a 35 U.S.C. 103 rejection based in part on inherent disclosure in one of the references). See also In re Grasselli, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983).

Moreover, "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

Therefore by teaching all the limitations of claims 1-4, Carpenter anticipates the instant invention as claimed.

Conclusion

Claims 1-4 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is (571) 272-3311. The examiner can normally be reached on 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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